SUMMARY OF PRODUCT CHARACTERISTICS.

1. Name of the medicinal product

Eflaron 250 Tablets.

2. Qualitative and quantitative composition

Each tablet contains: Metronidazole 250mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet for oral use.

Yellow coloured, biconvex tablets, plain on both sides.

4.0 Clinical particulars

4.1 Therapeutic indications

Anaerobic infections: gynaecological and intra-abdominal infections, infections of the CNS, pulmonary infections, septicaemia, endocarditis, infections caused by susceptible anaerobic bacteria: Bacteroides species, including B. fragilis group (B. distosonis, B. ovatus, B. thetaiotaomicron, B. vulgatus), Clostridium species, Eubacterium species, Peptococcus species, Peptostreptococcus species. Ulcerative gingivitis Infections caused by Trichomonas in both sexes. Amoebiasis Lambliasis and Helicobacter pylori eradication.

4.2 Posology and method of administration

Method of administration: Oral route

Dosage & Administration.

Anaerobic infections

Treatment of anaerobic infections (usually treated for 7 days and for 10 days in antibiotic – associated colitis), by mouth either 800mg initially then 400mg every 8 hours or 500mg every 8 hours.

Children: 7.5mg / kg every 8 hours.

Preventive treatment: adults and children more than 12 years old: (100ml) administered in slow intravenous drip infusion immediately before, or during operation; the same dose is repeated every 8 hours until oral treatment is possible (200mg to 400mg) 3 times daily. The treatment (intravenous and oral together) should not last more than a week.

Children less than 12 years old: 7.5mg/kg body weight (=1.5ml/kg) administered in slow intravenous drip infusion following the same schedule as in adults. Orally, a dosage of 3.7 to 7.5 mg/kg body weight is administered 3 times daily. The complete treatment lasts 7 days.

Trichomoniasis

Both partners should be treated simultaneously. Metronidazole is given by mouth either as a single 2-g dose, as a 2-day course of 800 mg in the morning and 1.2 g in the evening, or as a 7-day course of 600 mg to 1 g daily in two or three divided doses. If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended.

Children with trichomoniasis may be given a 7-day course of metronidazole by mouth as follows: 1 to 3 years, 50 mg three times daily; 3 to 7 years, 100 mg twice daily, and 7 to 10 years, 100 mg three times daily. An alternative children's dose is 15 mg/kg daily in divided doses for 7 days.

Amoebiasis

Metronidazole is given in doses of 400 to 800 mg three times daily by mouth for 5 to 10 days. Children aged 1 to 3 years may be given one-quarter, those aged 3 to 7 years one-third, and those aged 7 to 10 years one-half the total adult daily dose; alternatively 35 to 50 mg/kg daily in divided doses has been used. An alternative adult dose is 1.5 to 2.5 g as a single daily dose for 2 or 3 days.

Lambliasis:

Adults: 800mg daily, divided into two doses for a period of 5 days.

Children: 35mg to 50mg/kg body weight divided into two doses for a period of 5 days

Leg ulcers and pressure sores

400mg every 8 hours for 7 days by mouth.

Bacterial vaginosis

400 – 500mg twice daily for 5 - 7 days or 2g as a single dose by mouth.

Pelvic inflammatory disease

400 mg twice daily for 14 days

Acute ulcerative gingivitis

Adults: 200 - 250mg daily every 8 hours for 3 days
Children 1 – 3 years: 50mg daily every 8 hours for 3 days, 3 – 7 years 100mg every 12 hours and 7-10 years 100mg every 8 hours.

Acute oral infections

Adults: 200mg daily every 8 hours for 3 - 7 days
*Children 1 – 3 years:*50mg daily every 8 hours for 3 - 7 days,3 – 7 years 100mg every 12 hours and 7-10 years 100mg every 8 hours.

Surgical prophylaxis

Adults: 400 - 500mg daily every 2 hours before surgery; upto 3 further doses of 400 - 500 mg may be given every 8 hours for high – risk procedures.
Children: 7.5mg / kg 2 hours before surgery; upto 3 further doses of 7.5 mg / kg may be given every 8 hours for high – risk procedures

4.3 Contraindications

Hypersensitivity to metronidazole or other nitro- imidazole derivatives.
The first trimester of pregnancy.
If CNS disorders occur (ataxia, paraesthesia), treatment should be discontinued immediately. Concomitant administration of disulfiram is contraindicated too.

4.4 Special warnings and precautions for use

When warfarin or other anticoagulants are administered concomitantly, the dose should be adequately reduced. Patients should abstain from alcoholic beverages during treatment. Metronidazole is excreted with human milk and penetrates the placental barrier. The use of metronidazole during pregnancy and lactation is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction.

Interactions to be used with caution:
• Lithium: Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentration of lithium, creatinine, and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.
• Anticoagulants: Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. No interactions have been reported with anticoagulants of the heparin type. However, anticoagulant activity should be routinely monitored with these products.
• Alcohol: Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours after because of the possibility of a disulfiram-like reaction.
• Disulfiram: Psychotic reactions have been reported.
• Immunosuppressants: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.
Pharmacokinetic interactions:
• Antiepileptics: Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours. Metronidazole inhibits metabolism of phenytoin (increases plasma-phenytoin concentration). Primidone accelerates the metabolism of Metronidazole causing reduced plasma concentrations.
• Cytotoxics: Metronidazole inhibits metabolism of fluorouracil. Therefore, increased toxicity of fluorouracil can result. Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.
• Ulcer-healing drugs: Cimetidine inhibits the metabolism of metronidazole (increases plasma-metronidazole concentration).
• Oestrogens: broad spectrum antibiotics possibly reduce the contraceptive effect. See local/national guidelines or BNF for specific advice.
• Drug-lab modifications: Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole, depending on the method used.

4.6 Fertility, pregnancy and lactation.

There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. As with all medicines, metronidazole should not be given during pregnancy or during lactation unless it is considered essential, and in these circumstances the short, high-dosage regimens are not recommended.

Pregnancy

Metronidazole is contraindicated in the first trimester and should be used with caution in the second and third trimester when used to treat trichomoniais or bacterial vaginosis.

For all other indications Metronidazole should only be used if the benefits outweighs the risks or no other alternative is available especially in the first trimester.

Breast-feeding

It is advisable to stop breast feeding until 12 – 24 hours after Metronidazole therapy has been discontinued.

4.7 Effects on ability to drive and use machines.

Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects.

Frequency type and severity of adverse reactions in children are the same as in adults.

The frequency of adverse events listed below is defined using the following convention:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Serious adverse reactions occur rarely with standard recommended regimens.

Frequency, type and severity of adverse reactions in children are the same as in adults.

Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Blood and lymphatic system disorders:	
Very rare	Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known	Leucopenia, bone marrow depression disorders such as aplastic anaemia
Immune system class:	
Rare	Anaphylaxis
Not known	Angiodema, urticaria, fever
Metabolism and nutrition disorders:	
Not known	Anorexia
Psychiatric disorders:	
Very rare	Psychotic disorders, including confusion and hallucinations
Not known	Depressed mood
Nervous system disorders;	
Very rare	Encephalopathy (eg. confusion, fever, headache, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve in discontinuation of the drug, drowsiness, dizziness, convulsions, headaches
Not known	Depression, paraesthesia, during intensive and-or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced. Incoordination of movement, aseptic meningitis
Eye disorders:	

Eye disorders:	
Very rare	Diplopia, myopia
Not known	Optic neuropathy/neuritis
Ear and labyrinth disorders:	
Not known	Hearing impaired/hearing loss (including sensorineural), tinnitus
Gastrointestinal disorders:	
Not known	Unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances, diarrhoea, abdominal pain, anorexia
Hepatobiliary disorders:	
Very rare	Abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal, cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs
Skin and subcutaneous tissue disorders:	
Very rare	Skin rashes, pustular eruptions, pruritus, flushing
Not known	Erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption
Musculoskeletal, connective tissue and bone disorders:	
Very rare	Myalgia, arthralgia
Renal and urinary disorders:	
Very rare	Darkening of urine (due to metronidazole metabolite)

4.9 Overdose

Features:

Nausea, vomiting, diarrhoea, anorexia, metallic taste, headache, dizziness and occasionally insomnia and drowsiness. Transiently increased liver enzyme activities have been reported rarely.

Transient epileptiform seizures have been reported following intensive or prolonged therapy. Other adverse effects occurring in these circumstances include peripheral motor neuropathy, blood dyscrasias and liver damage.

The combination of alcohol and metronidazole has been said to cause disulfiram type reactions in about 10% of individuals with sudden onset of excitement, giddiness, flushing, nausea, headache, hypotension and dyspnoea. However the mechanism of this reaction has been questioned.

Treatment:

Unlikely to be required.

Disulfiram type reactions should be treated with intravenous fluids and plasma expanders if necessary. Symptomatic and supportive.

In more serious cases:

1. Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam (10-20mg in adults; 0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). Give oxygen and correct acid base and metabolic disturbances as required.
2. Other measures as indicated by the patient's clinical condition.

5. Pharmacological properties.

5.1 Pharmacodynamic properties.

***Pharmacotherapeutic group*:** Nitroimidazole derivatives.

ATC code: P01A B01.

Pharmacology:

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. It also has a radiosensitising effect on hypoxic tumour cells. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced. Metronidazole is active against several protozoa including Balantidium coli, Blastocystis hominis, Entamoeba histolytica, Giardia intestinalis (Giardia lamblia), and Trichomonas vaginalis. Most obligate anaerobic bacteria, including Bacteroides and Clostridium spp., are sensitive in vitro to metronidazole. It is bactericidal. It also has activity against the facultative anaerobes Gardnerella vaginalis and Helicobacter pylori and against some spirochaetes. Metronidazole has well-established bactericidal activity against obligate anaerobic bacteria in vitro, including the Gram-negative organisms Bacteroides fragilis and other Bacteroides spp., Fusobacterium spp., and Veillonella spp., and the Gram-positive organisms Clostridium difficile, Cl. perfringens, and other Clostridium spp., Eubacterium spp., Peptococcus spp., and Peptostreptococcus spp.; Propionibacterium and Actinomyces spp. are often resistant. It also has activity against the facultative anaerobe Gardnerella vaginalis, although its bactericidal effect is reported to be much slower than against obligate anaerobes, against some strains of Campylobacter spp. including C. fetus subsp. jejuni, and against Helicobacter pylori. The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of G. vaginalis.

5.2 Pharmacokinetic properties.

Metronidazole is readily and almost completely absorbed after oral doses. Peak plasma concentrations of about 6 and 12 micrograms/mL are achieved, usually within 1 to 2 hours, after single doses of 250 and 500 mg respectively. Some accumulation occurs and consequently there are higher concentrations when multiple doses are given. Absorption may be delayed, but is not reduced overall by food. Metronidazole benzoate given by mouth is hydrolysed in the gastrointestinal tract to release metronidazole, which in turn is then absorbed.

Peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been reported in patients given an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, cerebral abscesses; CSF, liver and liver abscesses, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins. Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The principal oxidative metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite), which has antibacterial activity and is detected in plasma and urine, and 2-methyl-5-nitroimidazole-1-acetic acid (the acid metabolite), which has virtually no antibacterial activity and is often not detected in plasma, but is excreted in urine. Small amounts of reduced metabolites, acetamide and N-(2-hydroxyethyl) oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora. The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe hepatic impairment; that of the hydroxy metabolite is prolonged in patients with substantial renal impairment. The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

5.3 Preclinical safety data

None known

6. Pharmaceutical particulars

6.1 List of excipients

MCC pH 102, Maize starch, Dye Tartrazine, PVP-K 30, Potassium sorbate, Purified water, Purified talc, Aerosil 200 and Sodium starch glycollate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protected from light.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Pack size: 1000's tablets in 500CC HDPE container along with literature insert.

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder

DAWA Limited
Plot No.7879/8, Baba Dogo Road Rd, Ruaraka.
P.O Box 16633-00620, Nairobi-Kenya.

8. Manufacturer

DAWA Limited
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9. Legal category

Prescription Only Medicine (POM).

10. Date of revision of the text

June 2019.